UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
[illegible]
[illegible]
www.[illegible]

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/591,737	06/12/2000	David T. Curiel	D6167CIP	3628

27851 7590 03/21/2002

BENJAMIN A. ADLER
8011 CANDLE LANE
HOUSTON, TX 77071

EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/591,737	CURIEL ET AL.	
	Examiner	Art Unit	
	Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-17,19-21,23-31 and 33-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-17,19-21,23-31 and 33-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____

4)☐ Interview Summary (PTO-413) Paper No(s) _____

5)☐ Notice of Informal Patent Application (PTO-152)

6)☒ Other *detailed action*

DETAILED ACTION

The Amendment filed on November 20, 2001 has been entered as Paper #6. Claims 2, 18, 22, and 32 have been canceled. Claims 1, 3-5, 9, 11, 14, 17, 21, 31, 33-36, 40, 43, 46-49, 53, and 55 have been amended. Claims 1, 3-17, 19-21, 23-31, and 33-56 are pending in the application and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

The prior rejection of claims 1-3, 5-56 under 35 U.S.C. 112, first paragraph are withdrawn in view of the amendment to claims that limit the gene delivery system to an adenovirus, a first antibody, or antigen-binding fragment thereof, that binds to a fiber-knob protein of an adenovirus, attached to a second antibody, or antigen-binding fragment thereof, that binds to CD40 antigen.

ENABLEMENT REQUIREMENT

A portion of the prior rejection of claims, drawn to broadly claimed two-antibody and Ady gene delivery system, or all immune system cells, are withdrawn in view of the

However, the prior rejection to claims 11-17, 19-21, 23, 24, 27-30, 40-45, and 53-56 stands for the reasons advanced on pages 8-12 of the prior Office action (paper No. 5), and applies to the newly amended claims.

The applicants argue in Paper # 6 that CD40-targeted virus demonstrated both dramatic and quantitative improvements in gene transfer compared to untargeted virus, that the claimed gene delivery systems also induce maturation of CD40+ cells as manifested by phenotypic and functional criteria, that the dendritic cells genetically modified by the claimed vector can efficiently initiate antigen specific immunity towards tumor antigen, it was also demonstrated that targeting of the claimed vector to CD40 imparts an advantage in a vaccination context over untargeted Adv. Thus, the scope of the claim is enabled.

The arguments have been carefully considered but found not persuasive. This is because the scope of the claims is much broader than those taught in the specification or recited *supra*.

The claims are directed to a method of genetically manipulating CD40+ immune cells in a human subject, for suppressing immune response, for enhancing dendritic cell-based vaccination, for the treatment of diseases including all types of cancer, infectious diseases, transplantation rejection, and autoimmune diseases via both *in vivo* and *ex vivo* gene therapy approaches, whereas the specification only illustrate a tumor reducing effect in an artificial tumor model in mice by intradermal injection of transfected DCs. As indicated in Paper 4 numerous teachings in the gene therapy art suggest that

vaccination, *McCluskie et al* (Mol Med 1999 May;5:287-300) teach UNFORTUNATELY, THE PROMISING RESULTS IN ANIMAL MODELS HAVE NOT BEEN REALIZED IN HUMAN TRIALS AND CONSIDERABLE EFFORT IS NOW BEING FOCUSED AT UNDERSTANDING THIS DIFFERENCE AND DEVELOPING WAYS OF IMPROVING THE EFFICACY OF DNA VACCINES". In the aspect of delivery of a therapeutic gene in humans, *Boucher et al* (J Clin Invest 1999 Feb; 103:441-5) teach "DESPITE AN IMPRESSIVE AMOUNT OF RESEARCH IN THIS AREA, THERE IS LITTLE EVIDENCE TO SUGGEST THAT AN EFFECTIVE GENE-TRANSFER APPROACH FOR THE TREATMENT OF CF LUNG DISEASE IS IMMINENT". In the treatment of an autoimmune disease, *Levine et al* (Mole Med Today 1999 Apr; 5:165-171) teach "A CAVEAT WITH ALL OF THESE STUDIES IS THAT THE IMMUNE RESPONSE IS ENORMOUSLY COMPLEX AND THAT SUBTLE DIFFERENCES BETWEEN SPECIES AND THE EXPERIMENTAL MODEL USED CAN RESULT IN DRAMATICALLY DIFFERENT RESULTS. FOR EXAMPLE, THERAPIES THAT PREVENT DIABETES IN RODENT MODELS OF DIABETES HAVE NOT BEEN EFFICACIOUS IN HUMANS". In the aspect of tumor immunotherapy, *Bodey et al* (Anticancer Res 2000;20:2665-76) teach, "THE THEORETICAL BASIS FOR ALL OF THESE APPROACHES IS VERY WELL FOUNDED. ANIMAL MODELS, ALBEIT HIGHLY ARTIFICIAL, HAVE YIELDED PROMISING RESULTS. CLINICAL TRIALS IN HUMANS, HOWEVER, HAVE BEEN SOMEWHAT DISAPPOINTING...", "THE CANCER VACCINE APPROACH TO THERAPY IS BASED ON THE NOTION THAT THE IMMUNE SYSTEM COULD POSSIBLY MOUNT A REJECTION STRENGTH RESPONSE AGAINST THE NEOPLASTICALLY TRANSFORMED CELL CONGLOMERATE. HOWEVER, DUE TO THE LOW IMMUNOGENICITY OF TUMOR ASSOCIATED ANTIGENS, DOWNREGULATION OF MHC MOLECULES, THE LACK OF ADEQUATE COSTIMULATORY MOLECULE EXPRESSION, SECRETION OF IMMUNE INHIBITORY CYTOKINES, ETC., SUCH EXPECTATION ARE RARELY FULFILLED..." (page 2665, column one). *Radoja et al* (Mol Med 2000;6:465-79)

mechanism how tumor antigen escape immune surveillance. "THE NOTION THAT A DEFICIT IN IMMUNE CELL FUNCTIONS PERMITS TUMOR GROWTH HAS RECEIVED EXPERIMENTAL SUPPORT WITH THE DISCOVERY OF SEVERAL DIFFERENT BIOCHEMICAL DEFECTS IN T LYMPHOCYTES THAT INFILTRATE CANCERS" (abstract). "ACCUMULATION OF CIRCULATING ANTITUMOR IMMUNOGLOBULIN G IN CANCER PATIENTS SHOW THAT THE PRIMING PHASE OF ANTITUMOR IMMUNE RESPONSE IS FUNCTIONAL DURING THE RELATIVELY SLOW PROCESS OF NASCENT TUMOR GROWTH...IN BOTH HUMAN CANCER PATIENTS AND RODENTS BEARING TUMORS OF DIFFERENT HISTOLOGIC ORIGIN, SYSTEMIC IMMUNITY IS NOT PROFOUNDLY SUPPRESSED..." "HOWEVER, INHIBITION OF A SPECIFIC ANTITUMOR IMMUNE RESPONSE HAS BEEN OBSERVED FREQUENTLY. A VARIETY OF MECHANISM HAVE BEEN PROPOSED TO ACCOUNT FOR DEFECTIVE ANTITUMOR IMMUNE RESPONSE, INCLUDING: SECRETION OF SUPPRESSIVE FACTORS IN THE TUMOR MICROENVIRONMENT, THE LACK OF EXPRESSION OF COSTIMULATORY SIGNALS ON TUMOR CELLS, INDUCTION OF REGULATORY T CELLS HAVING A SUPPRESSIVE PHENOTYPE, LOSS OF ANTIGEN PRESENTATION FUNCTION IN THE TUMOR, LOSS OF EXPRESSION OF HLA CLASS I ANTIGEN PRESENTING MOLECULES IN TUMORS, TUMOR-INDUCED T-CELL SIGNALING DEFECTS, LOSS OF TUMOR ANTIGEN EXPRESSION, IMMUNOLOGICAL IGNORANCE AND, SINCE MANY TUMOR ANTIGENS ARE EITHER UNMODIFIED SELF OR EPITOPES CLOSELY RELATED TO SELF, THE REDUCTION OF THE REPERTOIRE OF POTENTIAL HIGH AFFINITY ANTITUMOR T-CELL CLONES DURING T-CELL MATURATION IN THE THYMUS" (Introduction). As taught by *Boedy et al* and *Radoja et al*, the success or failure of cancer immunotherapy is determined by many distinct factors both from the nature of the antigen itself and the host immune responses. The etiology and the mechanism leading to a given cancer differ significantly among different cancer types. As of the post-filing date of the cited publications, failure far exceeds success in view of tumor

It is noted that in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 166 USPQ 18 (CCPA 1970). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, whether other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "IT IS WELL SETTLED THAT IN CASES INVOLVING CHEMICALS AND CHEMICAL COMPOUNDS, WHICH DIFFER RADICALLY IN THEIR PROPERTIES IT MUST APPEAR IN AN APPLICANT'S SPECIFICATION EITHER BY THE ENUMERATION OF A SUFFICIENT NUMBER OF THE MEMBERS OF A GROUP OR BY OTHER APPROPRIATE LANGUAGE, THAT THE CHEMICALS OR CHEMICAL COMBINATIONS INCLUDED IN THE CLAIMS ARE CAPABLE OF ACCOMPLISHING THE DESIRED RESULT." It is highly unpredictable whether the deficiency in cancer immunotherapy and other aspects of gene therapy as taught by those skilled in the art *supra* would be overcome by providing a bi-specific gene delivery system as instantly claimed. In conclusion, the specification fails to teach how to overcome the difficulties in the art, fails to demonstrate that any therapeutic effect was achieved in any recited disease in humans by the CD40 targeted Adenoviral vector.

Accordingly, in view of the quantity of experimentation necessary to determine the therapeutic effect for any given tumor and any given disease recited in the claims,

the claims directed to the use of [illegible] therapeutic [illegible]

undue experimentation for one skilled in the art to practice the claimed invention as they are broadly claimed.

For the reasons of record and those set forth above, the instant specification fails to meet the enablement requirement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because of the claim recitation "an adenovirus", which embraces a wild type adenovirus, which is not suitable to be used as a gene delivery vehicle in gene therapy in human.

Claim 1 is vague and indefinite because of the claim recitation "attached", the specification fails to defined the term, it is unclear what the term embraces, thus, the metes and bounds of the claim is unclear.

Contradictory to the remarks of Paper #6, the amended claims 11, 14, 17, 21, 40, 43, 53, and 54 still recite the limitation "such treatment". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 1, 5-7, 9-11, 13, 14, 16-18, 20-22, 24-31, 34-37, 40, and 42 under 35 U.S.C. 103(a) as being unpatentable over *Mendoza et el* (J Immunol 1997 Dec;159:5777-81) in view of *Christ et al* (Immunol Lett 1997 Jun;57:19-25), are withdrawn in view of the amendments.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-10, 25, 26, 31, 33-37, and 46-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,284,742. Although the conflicting claims are not

identical, they are not patentably distinct from each other because the instant claims encompass claims 1-6 of the cited patent.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present application and the claims 1-6 of the cited patent are each drawn to a gene delivery system comprising an adenovirus, a first antibody which specifically binds a fiber-knob protein of said adenovirus, and a second antibody which specifically binds the CD40 antigen.

The system of the present application and the cited patent differ one from the other in that the first and second antibodies in the cited patent are genetically fused together, wherein the instant claim 1 recites that that "said first antibody *is attached* to a second antibody", which embraces "genetically fused together" as claim 3 recites "the gene delivery system of claim 1, wherein said first antibody and second antibody are genetically fused together".

Moreover, considerable overlap is also noted in present claim 1 and claim 1 of the cited patent. Claim 1 of the cited patent recites "a composition for delivery of a gene of interest to *antigen presenting cells*", the instant claim 1 recites a gene delivery for "CD40+ immune cells". Because CD40 antigen are present on the surfaces of B cells, dendritic cells and macrophages, which function as antigen presenting cells in the host immune system, thus, the targeting cells of the gene system are virtually the same in the present application and the cited patent.

Accordingly, the claimed system in the cited patent and the present application

Claims 1, 3-10, 25, 26, 31, 33-39, and 46-52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,284,742 in view of *Krul et al* (Cancer Immunol Immmunother 1996;43:44-48).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present application and the claims 1-6 of the cited patent are each drawn to a gene delivery system comprising an adenovirus, and a bispecific targeting component, wherein the adenoviral vector encodes a gene of interest selected from the group consisting of a gene encoding a tumor antigen, or an infectious agent.

The system of the present application and the cited patent differ one from the other in that the cited patent does not recite human papillomavirus type 16 E7 antigen.

However, *Krul et al* teach a HPV recombinant vaccine expressing HPV type 16 E6 and E7 proteins as a vaccine for cervical carcinomas.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the gene delivery system taught by the cited patent by simply including a HPV16 E7 antigen as the gene of interest as taught by *Krul et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the CD40-targeting gene delivery system would enhance the vaccine effect. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Accordingly, the claimed system in the cited patent and the present application are obvious variants. Therefore, the inventions as claimed are co-extensive.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
March 11, 2002

JAMES KETTER
PRIMARY EXAMINER